REMARKS

Claims 1-49 are pending in this application. Claims 1-46, and 49 have been withdrawn from consideration as being drawn to the non-elected invention. Claims 47 and 48 have been rejected. None of the claims have been objected to. Applicants have cancelled Claims 1-46, and 49, amended Claims 47 and 48 and have added new Claims 50-73. The added claims 50-55 are well based on language in the patent specification page 5, lines 1-4. The amendment to incorporate the language "substantially purified form" in claims 47 and 48 is based on page 4, lines 6-20. Basis for added claims 56-61 is found in page 4, lines 1-5. Basis for added claims 62, 63, 70 and 71 is found in page 6, lines 6-9. Basis for added claims 64-67 is found in page 5, lines 1-28. Basis for added claims 68-69 and 72-73 is found in page 9, lines 6-14.

In view of the following amendment and response, the Applicants believe the claims presented herein are allowable. Reconsideration is respectfully requested.

REJECTIONS UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 47 and 48 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention.

First, the examiner questions whether parenthetical notation of "weight/weight" is intended as a claim limitation or is merely an example of means by which one of ordinary skill could measure whether excess of sterol has been added to the formulation. Secondly, the Examiner questions if the excess sterol is an excess over the entire weight of the formulation to which it is added, or if the weight of the sterol need only be an excess over the weight of QS21. The Examiner requests clarification to these two points.

Applicants respond that the notation is the basis upon which the amounts of components are measured. Furthermore, the notation is intended to be the ratio of amounts of one component (QS21) over another (sterol).

The Applicants respectfully submit that in view of the forgoing remarks, the Applicants have overcome the Examiner's rejection under 35 U.S.C. §112, second paragraph, and the rejection should be withdrawn.

REJECTIONS UNDER 35 U.S.C. §102(b)

Claims 47 and 48 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by the teachings of Lipford, *et al.* (Vaccine 12(1): 72-80)(hereinafter referred to as

"Lipford") in light of the teachings of Kensil, *et al.* (U.S. Patent Number 5,583,112)(hereinafter referred to as "Kensil").

The wording of "wherein the QS21 is present in substantially purified form" has been added to claims 47 and 48. Lipford makes use of Quil A and not QS21 "in substantially purified form" as is the subject of the amended claim. The "substantially purified form" language excludes Quil A since Quil A contains 20 or so other components besides QS21 (see Table 1 of Kensil, column 13). Thus the amendments now obviate 35 U.S.C. 102(b) rejection.

Claims 47 and 48 were also rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Mackenzie, et al. (EP Publication Number EP 0 415 794)(hereinafter referred to as "Mackenzie") in light of teachings of Kensil.

Mackenzie makes use of Quil A and not QS21 "in substantially purified form" as is the subject of the amended claims. The "substantially purified form" language excludes Quil A since Quil A contains 20 or so other components besides QS21 (see Table 1 of Kensil, column 13). Thus the amendments should now obviate 35 U.S.C. 102(b) rejection.

It should further be noted that the formulation of Lipford disclosed on page 74 bottom of left column to top of right column contains 5.0 mg cholesterol and at most 0.4mg Quil A (the amount of Quil A is 1ml less "a minimal volume" times the concentration of 0.4 mg/ml) . Quil A contains only 3.7% QS21 (see Kensil column 13 lines 27). Therefore the ratio of sterol to QS21 is at least 5:0 / 0.4 * 0.037 i.e. at least 338. This falls outside of the claimed weight/weight range of newly added claims 50-55.

The Applicants respectfully submit that in view of the forgoing remarks, the Applicants have overcome the Examiner's rejection under 35 U.S.C. §102(b), and the rejections should be withdrawn.

REJECTIONS UNDER 35 U.S.C. §103(a)

Claims 47 and 48 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Lipford, *et al.* (Vaccine 12(1): 72-80)(hereinafter referred to as "Lipford") in light of the teachings of Kensil, *et al.* (U.S. Patent Number 5,583,112)(hereinafter referred to as "Kensil").

Examiner alleges that it would have been obvious to substitute QS21 for Quil A in the complexes described by Lipford, based on the fact that Kensil teaches that QS21 has potent adjuvant activity, and that the resultant composition would ***inevitably*** exhibit the properties of reduced reactogenicity and hydrolysis of QS21.

Firstly, the Examiner is respectfully reminded that which is *(arguendo)* inherent in the prior art, if not known at the time of the invention, cannot form a proper basis for rejecting the claimed invention as obvious under 35 U.S.C. 103. See In re Shetty, 566 F.2d 81, 86, 195 U.S.P.Q. 753, 756-57 (C.C.P.A. 1977). More detailed arguments to rebut the Examiner's basis of rejection are provided below.

Claim 47 (and dependent claims)

Kensil discloses that injection of animals with Quil A causes severe symptoms lasting 48 hours whereas injection with QS21 caused the animals to be "mildly ill" (see column 27 lines 15-18). Quil A in particular appeared to cause damage to the liver. In essence Kensil teaches that QS21 is less toxic than Quil A but nevertheless is still toxic. Lipford contains no discussion concerning QS21 or toxicity in the use of Quil A or QS21.

By contrast the present patent application discloses convincing evidence that use of excess sterol such as cholesterol in conjunction with QS21 causes a significant improvement in reactogenicity, and specifically improves the symptoms of redness, necrosis and toxicity in the muscle at the site of injection, as compared with use of QS21 alone (see the first table on page 15 of the specification).

The Examiner's allegation that a skilled person would combine Kensil with Lipford in the expectation of producing an adjuvant composition which has ***reduced reactogenicity*** characteristics compared with QS21 used alone cannot be justified since neither document mentions how the reactogenicity (toxicity) of QS21 may be reduced. Furthermore, Examiner's contention that a skilled person would combine the two documents and would therefore inherently benefit from the property is flawed since it omits the necessary identification of a motivation to combine the documents in expectation of obtaining the claimed advantage (i.e. improved reactogenicity). The Court in In re Napier, 55 F.3d 610, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995) emphasized "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination."

Claim 48 (and dependent claims)

Kensil at column 21 (line 17 et seq) discloses that QS21 can be hydrolysed by alkali. At column 28 lines 9-16 it is stated that adjuvant activity is lost or altered in the hydrolysis product. However this document contains no teaching as to how the hydrolysis can be prevented. Lipford does not mention QS21 and accordingly does not mention the hydrolysis of QS21 or how to prevent it.

By contrast the present application discloses convincing evidence that use of excess sterol such as cholesterol in conjunction with QS21 causes a significant reduction in susceptibility of QS21 to hydrolysis. The hydrolysis of QS21 under certain conditions is shown in Figure 2 and, as explained in the specification on page 14, paragraphs 19-30, the hydrolysis under the same conditions was abolished by addition of excess cholesterol.

The Examiner's allegation that a skilled person would combine Kensil with Lipford in the expectation of producing an adjuvant composition which has better stability characteristics cannot be justified since neither document discusses how to deal with the hydrolysis problem of QS21. As before, the Examiner's contention that a skilled person would combine the two documents and would therefore inherently benefit from the property is flawed since it omits the necessary identification of a motivation to combine the documents in expectation of obtaining the claimed advantage (i.e. hydrolysis resistance).

The Applicants respectfully submit that in view of the forgoing remarks and the claims as amended, the Applicants have overcome the Examiner's rejection under 35 U.S.C. §103(a), and the rejections should be withdrawn.

The Applicants reserve the right to prosecute, in one or more patent applications, the claims to non-elected inventions, the claims as originally filed, and any other claims supported by the specification. The Applicants thank the Examiner for the Office Action and believe this response to be a full and complete response to such Office Action. Accordingly, favorable reconsideration and allowance of the pending claims is earnestly solicited.

If it would expedite the prosecution of this application, the Examiner is invited to confer with the Applicants' undersigned agent.

Respectfully submitted,

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